plasma or serum. Phenytoin, carbamazepine, and sodium valproate are heavily protein bound, but only the free drug fraction is in equilibrium with the brain and pharmacologically active. Though variation in protein binding of drugs is usually not clinically important, upsets in the relation may occur in hepatic and renal failure[5] and pregnancy and because of drug interaction—for example, phenytoin with sodium valproate. The salivary concentrations of phenytoin and carbamazepine correlate well with free drug concentrations, but this is not so for sodium valproate. Salivary measurements may thus be more meaningful, but they are not used by many laboratories. Measurement of free drug concentrations by equilibrium dialysis or ultrafiltration techniques are expensive and not readily available.

Even when concentrations of free drugs and their metabolites in blood are known important pharmacodynamic considerations may alter the relation between the blood concentration and the therapeutic effect. Thus for sodium valproate the onset of action is slower and longer lasting than can be explained by the pharmacokinetics of the drug.[6] Similarly tolerance to the neurotoxicity and therapeutic effects of benzodiazepines and barbiturate drugs must be caused by unexplained changes in drug-receptor interaction.

There are further fundamental biological reasons for doubting the value of routine monitoring of blood concentrations of antiepileptic drugs. The upper limit of a therapeutic range may be defined as the concentration of the drug at which toxic effects are likely to appear. The most consistent relation between the serum concentration and toxic effect is for phenytoin, but even with this drug some patients may tolerate and indeed require serum concentrations above 20 μg/ml.[7] For sodium valproate, phenobarbitone, and carbamazepine there is a wide variation in individual tolerance of serum concentrations.

The lower limit of the therapeutic range is even more difficult to define, and many patients have epilepsy that is controlled by anticonvulsant serum concentrations well below the optimal range.[8,9] Even for one patient the threshold for suppressing tonic clonic seizures may differ from that for suppressing partial seizures.[10] Unquestioning acceptance of therapeutic ranges creates problems: patients with satisfactory control of seizures and low blood concentrations of drugs may have their doses needlessly increased, and patients who tolerate and need high blood concentrations may have their doses reduced. Treating patients is much more important than treating blood concentrations.

Monitoring blood concentrations of anticonvulsants remains important in clinical trials of antiepileptic drugs, but routine monitoring should be restricted to certain categories of patients: firstly, those receiving phenytoin or multiple drug treatment in whom dosage adjustment is necessary because of dose related toxicity or poor seizure control; secondly, mentally retarded patients in whom the assessment of toxicity may be difficult; thirdly, patients with renal or hepatic disease and perhaps pregnant patients,[11] in whom monitoring of free drug concentrations may be indicated; and, finally, patients who may not be complying with treatment.

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Original pack dispensing

In Britain a pharmacist either dispenses a medicine in the manufacturer's original pack or, more often, takes the product from a large container and "repackages" it in a smaller one. British pharmaceutical manufacturers are campaigning for dispensing of medicines in original packs to become the norm rather than the exception, a move that would bring Britain into line with virtually all other countries in the European Community.

The trend has already been set, and more and more manufacturers have introduced packs that can be dispensed directly to the patient. Good examples are calendar packs for oral contraceptives and some antihypertensives, strip or foil packs of tablets or capsules, pressurised inhalers for anti-asthma medication, and tubes of skin creams or ointments. About 40% of prescriptions are now dispensed in this way, but, as original pack dispensing has advantages for doctors, pharmacists, and patients, we regret that some 60% are not. A recent survey by Milpro of some 200 general practitioners showed that most saw advantages in original pack dispensing, while a few were worried about loss of flexibility of dosage.

The Association of the British Pharmaceutical Industry aims at full introduction of original pack dispensing within two to three years. Other organisations—such as the Medicines Commission, the BMA, and the Pharmaceutical Society—support the association, and the Department of Health and Social Security is keen to introduce "tamper evident" packaging after experiences of deliberate contamination of medicines. In practice a "tamper evident" pack can only be the manufacturer's original pack delivered unopened to the patient. Manufacturers, prescribers, and dispensers all support two basic types of pack: a short term treatment pack for seven days' treatment or the normally recommended time for a course of treatment; and a long term pack for one month's treatment.

The advantages of original pack dispensing are many. The identity of the product, batch, and company are preserved, which may have medicolegal importance and also allows more effective recall. The product can be more rapidly identified in cases of accidental overdose. The security and stability of the product are improved, and "tamper evident" and child resistant packs can be developed. Patient compliance may be better and dispensing faster and more efficient. Dispensing errors and mislabelling should also be avoided.

Original packs help maintain the stability and integrity of the medicine, and storage in the manufacturer's pack ensures that it reaches the patient in the container designed for the purpose. The package also carries the batch number and expiry date. Medicines repacked in a pharmacist's container can have no such guarantees. The batch number has important advantages for patient safety, and over the counter medicines must by law be labelled with a batch number; yet the usually more potent dispensed products are not required to bear such identification on the package received by the patient. Dispensing from bulk containers into identical bottles may also confuse patients because so many medicines look the same.

Now that the European Community directive on product liability has been adopted its requirements will have to be introduced into British laws. The directive introduces strict liability, which means that a patient damaged by a medicine will no longer have to show that its manufacturer or supplier has been negligent. An important provision in the directive is that if the claimant does not know the source of the product and his immediate supplier is unable or unwilling to tell him then the immediate supplier himself will be liable. This might be a dispensing doctor or a pharmacist, and both groups have been warned. Original pack dispensing would obviously mean that the manufacturer could be identified.

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Are pesticides carcinogenic?

The House of Commons Agriculture Committee is inquiring into the effects of pesticides on human health, reflecting widespread public concern about such chemicals. Cancer is among the more serious diseases that have been linked with pesticides. To date 49 insecticides, herbicides, fungicides, and related compounds have been reviewed by the International Agency for Research on Cancer in its series of monographs on chemical carcinogenicity.[1] It judged 11 to be carcinogenic in animals but did not find conclusive evidence that any were carcinogenic in man.

Epidemiological data on pesticides are few, and those that there are give a clouded picture. A good example is the continuing controversy over the alleged carcinogenicity of phenoxy herbicides (2,4,5-T, 2,4-D methylchlorophenoxyacetic acid, etc). Three Swedish case-control studies suggested that exposure to these compounds carried about a sixfold increase in risk for soft tissue sarcoma, Hodgkin's disease, and non-Hodgkin's lymphoma,[2-4] but similar surveys in New Zealand found only weak associations with these tumours.[5 6] Several investigators have followed up workers employed in the manufacture and use of phenoxy acids and found small excesses of soft tissue sarcoma but not of lymphoma.[7-11] Now a large case-control study in Kansas has failed to show an association with soft tissue sarcoma or Hodgkin's disease but does show an increased risk of non-Hodgkin's lymphoma with an impressive dose-response relation.[12]

How should regulatory bodies react to this conflicting evidence? Simply to dismiss the epidemiological data as untrustworthy would be wrong. Discrepant findings may arise by several mechanisms: chance variation; bias in the study methods; confounding exposures; and, importantly, differences in the quality, quantity, and timing of exposures. A proper evaluation must consider all of these possible explanations and arrive at a synthesis. Uncertainties will remain, but the range of uncertainty may not be large when viewed in terms of individual attributable risk (by how much might exposure to phenoxy acids increase a person's chances of developing cancer?) and population attributable risk (by how much might the use of phenoxy acids increase the incidence of cancer in the community as a whole?)

It is on these measures as opposed to relative increases in risk that regulatory decisions should be based.

Some would argue for erring on the side of safety—if a chemical is suspected of causing cancer it should be banned. This argument takes no account, however, of the benefits to health from use of pesticides—for example, through improved food production and the control of arthropod borne disease. No chemical can ever be proved totally safe, and, as in therapeutics, decisions on regulating pesticides must balance hazards against benefits.

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Coronary prevention in Britain: action at last?

The recent report of the British Cardiac Society working group on coronary prevention[1] could herald the start of a planned national attack on ischaemic heart disease, with serious commitment of time and staff rather than costless rhetoric. It ends a long period of bickering over such impractical issues as the choice between high risk and mass strategies and whether the national diet should contain 30% or 40% of energy derived from fat, leaving coronary prevention as everybody's business but no one's responsibility.